

**HED DOC. NO. 012729**

Date: August 7, 1998

**MEMORANDUM**

**SUBJECT:** ***BUTYLATE***- Report of the Hazard Identification Assessment Review Committee.

**FROM:** Paul Chin  
Reregistration Branch I  
Health Effects Division (7509C)  
and  
Jess Rowland, Executive Secretary  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)

**THROUGH:** K. Clark Swentzel, Chairman,  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)

**TO:** Virginia Dobozy, Risk Assessor  
Reregistration Branch I  
Health Effects Division (7509C)

**PC Code: 041405**

On June 9 and July 21, 1998, HED's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **Butylate** and selected the toxicological endpoints for acute and chronic dietary, occupational and residential (dermal and inhalation) exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to **Butylate** as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

### Committee Members in Attendance

Members present were Clark Swentzel, Bill Burnam, Karl Baetcke, Sue Makris, Jess Rowland (Executive Secretary) and John Redden. Members in an absentia were Mike Metzger, Karen Hamernik and Melba Morrow. Data were presented by Paul Chin of Reregistration Branch I.

Also, in attendance were Virginia Dobozy and Whang Phang.

Data Presentation:

and

Report Presentation

\_\_\_\_\_  
Paul Chin  
Toxicologist

Report Concurrence:

\_\_\_\_\_  
Jess Rowland  
Executive Secretary

## **I. INTRODUCTION**

Butylate (SUTAN Technical; S-ethyl diisobutyl thiocarbamate) is a selective herbicide registered for use on field corn, sweet corn, and popcorn. There are no registered residential uses at the present time. Therefore, risk assessments are applicable only for occupational exposures. There is a potential for mixer/loader/applicator exposure to butylate sprays as well as a potential for exposure to contaminated soil with respect to individuals incorporating the herbicide into the soil. The exposure route for both groups of handlers is via the dermal and inhalation routes.

The HED RfD/Peer Review Committee on October 15, 1992 has established a RfD of 0.05 mg/kg/day using an uncertainty factor of 100. This was based on a NOEL of 5 mg/kg/day for increased relative liver weights observed in males at 25 mg/kg/day in a 12-month feeding study in dogs. In addition, the HED RfD/Peer Review Committee classified **Butylate as a Group E carcinogen** based on lack of evidence of carcinogenicity in rats (HED Doc. No. 004590 and 005795) and mice (HED Doc. No. 003070 and 003830).

## **II. HAZARD IDENTIFICATION**

### **A.1 Acute Reference Dose (RfD) Population Subgroup: Females 13+**

Study selected: Developmental Toxicity Study in Rats

Guideline #: 83-3(a)

MRID No.: 00131032

Executive Summary: In a developmental toxicity study, butylate technical (98.2%) was administered to female Sprague-Dawley rats (26/dose) by oral intubation at doses of 0, 40, 400, or 1000 mg/kg/day from gestation days 6 through 20. No adverse effects were seen in mothers or offspring at 40 mg/kg/day. At 400 mg/kg/day, decreases in body weight (4%) and body weight gain (55%), decrease in food consumption, and increase in relative liver weight were observed. At 1000 mg/kg/day, an increase in early resorption was observed. At 400 and 1000 mg/kg/day, dose-related decreases in fetal body weights, increased incidences of hematomas of the thoracic spinal region and misaligned sternebrae were observed. In addition, there was also an increased incidence of incompletely ossified sternebrae in the high dose fetuses. The NOEL for maternal toxicity was 40 mg/kg/day. The LOEL for maternal toxicity was 400 mg/kg/day based on decreases in body weight, body weight gain, food consumption, and an increase in relative liver weight. **The NOEL for developmental toxicity was 40 mg/kg/day. The LOEL for developmental toxicity was 400 mg/kg/day based on decreased fetal weights and increased incidences of misaligned sternebrae.** This study is classified Acceptable/Guideline and satisfies the guideline data requirement for a developmental study (83-3a) in rats.

Dose and Endpoint for Risk Assessment: Developmental NOEL=40 mg/kg/day based on decreased fetal weights and increased incidences of misaligned sternebrae at 400 mg/kg/day (LOEL).

Comments about Study/Endpoint: The developmental effects are presumed to occur following a single exposure (dose) and thus are relevant for acute dietary risk assessment. Since these are *in utero* effects, they are applicable for risk assessments only for Females 13 +.

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for inter-species extrapolation (10 x) and intra-species variability (10 x).

$$\text{Acute RfD} = \frac{40 \text{ mg/kg}}{100 \text{ (UF)}} = 0.4 \text{ mg/kg}$$

**This Risk Assessment is Required.**

## **A.2 Acute Reference Dose (RfD) General Population including Infants and Children**

Study Selected: Acute Neurotoxicity Study in Rats Guideline #: 81-8

MRID No.: 43514101 and 43967901

Executive Summary: In an acute neurotoxicity screening study, butylate technical (95.7% a.i.) in corn oil was administered to Sprague-Dawley rats (10/sex) by oral intubation at single doses of 0, 200, 600, or 2000 mg/kg. Animals were monitored for neurotoxic responses at 5-6 hours postdosing and on days 8 and 15. At termination, histopathology assessments were made. At 600 mg/kg there was lacrimation (1/10 males), oral-nasal staining (1/10 males) and urinary incontinence (1/10 males and 2/10 females). At 2000 mg/kg there was neuronal cell necrosis in the brain (2/5 males), degenerate nerve fibers in the sciatic nerve (1/5 male and 2/5 females), salivation (3/10 males and 1/10 females) and tiptoe gaits (1/10 females). In addition, at this dose, there was lacrimation (1/10 males), oral-nasal staining (2/10 males), urinary incontinence (7/10 females), decreased body weight (5% at day 8 and 4.2% at day 16) and decreased food consumption in males (15% at week 1) and females (12% and 16% at weeks 1 and 2, respectively). [There are some indications of transient clinical signs in one male (oral-nasal staining) or two females (urinary incontinence) at 600 mg/kg. At 2000 mg/kg, the frequency of oral-nasal staining increased only slightly to two males and urinary incontinence to 7 females. Since these effects were transient, it is not considered to be of a magnitude or severity to justify setting the LOEL at 600 mg/kg.]

**The NOEL for acute neurotoxicity was 600 mg/kg. The LOEL for acute neurotoxicity was 2000 mg/kg based on sciatic nerve effects, neuronal cell necrosis, body weight decrease, and clinical signs of toxicity. This study is acceptable/guideline and satisfies the guideline data requirement for an acute neurotoxicity screening battery (81-8).**

Dose and Endpoint Proposed for Risk Assessment: NOEL=600 mg/kg/day based on sciatic nerve effects, neuronal cell necrosis, body weight decrease, and clinical signs of toxicity at 2000 mg/kg/day (LOEL).

Uncertainty Factor: An uncertainty factor of 100 was applied to account for inter-species extrapolation (10 x) and intra-species variability (10 x).

$$\text{Acute RfD} = \frac{600 \text{ mg/kg}}{100 \text{ (UF)}} = 6 \text{ mg/kg/}$$

Comments about Study/Endpoint: none

**This Risk Assessment is Required.**

## **B. Chronic Dietary (Chronic RfD)**

Study Selected: 12-Month Dog Feeding Study

Guideline #: 83-1 (b)

MRID No.: 40389101

Executive Summary: In a chronic toxicity study, gelatin capsules containing 0, 5, 25, or 100 mg/kg/day of butylate technical (100% a.i.) was administered to Beagle dogs (5/sex/dose) for 12 months. There was no statistically significant treatment related effects on body weight. In male dogs at 25 mg/kg/day, body weight measured at weeks 39 and 52 was only 4.6 and 6.3% lower compared to the controls, respectively. There was a statistical increase in relative liver weight in male dogs at 25 mg/kg/day. At 100 mg/kg/day, body weight measured at weeks 39 and 52 was reduced in males (4.6-8.4%) and females (4.8%). Body weight gain (not statistically significant) was reduced in males (17-50%) at 25 mg/kg/day and males (26-50%) and females (20-30%) at 100 mg/kg/day. Both sexes of dogs at 100 mg/kg/day had increased platelet count, increased alkaline phosphatase activity, and increased relative and absolute liver weights. In the 100 mg/kg/day group, relative and absolute thyroid/parathyroid weights were increased in males only. Additionally hepatocellular vacuolation/vesiculation was observed in 2/5 males (0/5 in controls).

**The NOEL for systemic toxicity in males was 5 mg/kg/day. The LOEL for systemic toxicity was 25 mg/kg/day based on decreased body weight gain (not statistically significant) and increased relative liver weight in male dogs. The NOEL for systemic toxicity in females was 25 mg/kg/day; the LOEL was 100 mg/kg/day based on decreased body weight gain, changes in clinical pathology parameters and increased absolute and relative liver and thyroid/parathyroid weights.** This study is classified acceptable/guideline and satisfies the guideline data requirement for a chronic toxicity study (83-1) in dogs.

Dose and Endpoint for Establishing RfD:

NOEL of 5 mg/kg/day based on increased relative liver weight in 25 mg/kg/day males.

Uncertainty Factor(s): An uncertainty factor of 100 was applied to account for inter-species

extrapolation (10 x) and intra-species variability (10 x).

$$\text{Chronic RfD} = \frac{5 \text{ mg/kg/day}}{100 \text{ (UF)}} = 0.05 \text{ mg/kg/day}$$

Comments about Study/Endpoint: The HIARC concurred with the RfD established in 1992.

### **C. Occupational/Residential Exposure**

**There are no registered residential uses at the present time.** Therefore, the following risk assessments are applicable only for occupational exposures.

#### **1. Dermal Absorption**

No dermal absorption studies are available. Although an oral (developmental) and dermal (21-day) studies were available in the same species (rabbits) a dermal absorption factor could not be estimated (calculated) due to the lack of a LOEL in the 21-day dermal study. Therefore, the Committee recommended a dermal absorption rate of 100% (default value).

Dermal Absorption Factor: 100%

#### **2. Short-Term Dermal - (1-7 days)**

Study Selected: Developmental Rat Study

Guideline #: 83-3(a)

MRID No.: 00131032

Executive Summary: See Acute Dietary (Females 13 +)

Dose and Endpoint for Risk Assessment: Developmental NOEL=40 mg/kg/day based on decreased fetal weights and increased incidences of misaligned sternebrae at 400 mg/kg/day (LOEL).

Comments about Study/Endpoint: The HIARC did not use the 21-day dermal toxicity study in rabbits because: 1) only two dose levels were tested in the study; 2) a LOEL was not established (i.e., the highest dose tested was not adequate to assess dermal or systemic toxicity); 3) the concern for the developmental effects seen in the developmental toxicity rats which are not evaluated in the 21-day dermal study; and 4) this dose/endpoint will provide adequate protection for female workers. Since an oral NOEL was selected for this risk assessment, a dermal absorption factor of 100% (default) should be used in risk assessments.

**This risk assessment is required.**

### 3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: Developmental Rat Study

Guideline #: 83-3(a)

MRID No.: 00131032

Executive Summary: See Acute Dietary (Females 13+)

Dose and Endpoint for Risk Assessment: Developmental NOEL=40 mg/kg/day based on decreased fetal weights and increased incidences of misaligned sternebrae at 400 mg/kg/day (LOEL).

Comments about Study/Endpoint: The HIARC did not use the 21-day dermal toxicity study in rabbits because: 1) only two dose levels were tested in the study; 2) a LOEL was not established (i.e., the highest dose tested was not adequate to assess dermal or systemic toxicity); 3) the concern for the developmental effects seen in the developmental toxicity rats which are not evaluated in the 21-day dermal study; and 4) this dose/endpoint will provide adequate protection for female workers. Since an oral NOEL was selected for this risk assessment, a dermal absorption factor of 100% (default) should be used in risk assessments.

**This risk assessment is required.**

### 4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None.

MRID No.: None.

Executive Summary: None.

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study/Endpoint: Based on the current use pattern (preplant/3-6 lb a.i./acre/1-application per season), there is minimal concern for potential Long-Term dermal exposure/risk.

**This risk assessment is NOT required.**

### 5. Inhalation Exposure (Short-and Intermediate-Term)

Except for an acute inhalation toxicity study, for which butylate is placed in Toxicity Category III (LC50 > 1.64 mg/L), no other studies are available via this route. Therefore, the HIARC selected the oral NOELs inhalation risk assessments. Since the doses identified for inhalation risk assessments are from oral studies route-to-route extrapolation should be as follows

- Step I. Convert the inhalation exposure component (i.e.,  $\mu\text{g a.i./day}$ ) using a 100% absorption rate (default value) and an application rate to an **equivalent oral dose** ( $\text{mg/kg/day}$ )
- Convert the dermal exposure component (i.e.,  $\text{mg/kg/day}$ ) using a 100% dermal absorption factor and an application rate to an **equivalent oral dose**.
- Step II Combine the converted oral equivalent doses (Steps I & II) for total (dermal + inhalation) exposure.
- Step III Compare the combined dose (Step II) to the oral NOEL of 40  $\text{mg/kg/day}$  to calculate the MOE's for both Short-Term and Intermediate-Term exposures.

Based on the use pattern, Long-Term inhalation exposure risk assessment is not required.

**This risk assessment is required.**

#### **D. Recommendation for Aggregate (Food, Water and Dermal) Exposure Risk Assessments**

Since there are no registered residential uses at the present time, aggregate exposure risk assessment will be limited to Food + Water only.

#### **E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments**

A MOE of 100 is adequate for occupational (dermal and inhalation) exposure risks. There are no registered residential uses at the present time, therefore, an MOE is not required for residential exposures.

### **III. CLASSIFICATION OF CARCINOGENIC POTENTIAL**

#### **A. Combined Chronic Toxicity/Carcinogenicity Study in Rats**

MRID No. 00125678, 41014901 and 41249501; Accession No. 249390-249403 and 261476

Discussion of Tumor Data There was a significant increase in the combined incidence of periportal hepatocellular hypertrophy and hepatocytomegaly in the livers of males receiving 400  $\text{mg/kg/day}$  (22.9% vs. 4.3% for controls) while the incidences of combined lesions in males at 50, 100, and 200  $\text{mg/kg/day}$  were 5.8%, 6.2%, and 8.6%, respectively. The performing lab's (Bio/dynamics) historical control ranges for the combined incidence of periportal hepatocellular hypertrophy and hepatocytomegaly for males in 14 studies was 0-22.8% (mean, 6.2%). Incidences of lesions among treated females at any dose level were not significantly different from controls.

There was also statistically significant ( $p < 0.05$ ) increased incidences (12.8%) over concurrent controls (2.9%) of “neoplastic nodules”(hepatocellular adenomas) in the livers of the high-dose males (400 mg/kg/day). The incidence rate of hepatocellular adenomas in the HDT males (12.8%) was within the performing lab’s (Bio/dynamics) historical control range for this type of lesion as reported in 13 previous studies, namely 2.5 to 17.1% (mean, 7.18%). There was no comparable increase in malignant neoplasms (“hepatocellular carcinomas”), nor in ratios of benign to malignant lesions. **The study demonstrated that butylate was not carcinogenic in rats at the doses tested.**

[Note: Based on the above data, the HED Panel at an abbreviated Cancer Peer Review meeting concluded that the increased incidences of hepatocellular adenomas in the HDT males were considered equivocal and not a biologically relevant evidence for the carcinogenicity of butylate in the rat (memo from I. Mauer, HED to R. J. Taylor, Registration Division, HED Document No. 009449, dated Feb. 23, 1990)].

#### Adequacy of the Dose Levels Tested

The dose levels are adequate based on decreased body weight gains in both male and female rats at 100 mg/kg/day or higher.

#### **B. Carcinogenicity Study in Mice**

MRID No. 0035844.

Discussion of Tumor Data. No significant increased in tumors were observed.

Adequacy of the Dose Levels Tested The dose levels are adequate based on decreased body weights and increased incidences of kidney findings (amyloidosis, chronic nephritis, and lymphocytic foci) in females at 80 mg/kg/day (the mid dose group) and based on decreased food consumption, decreased kidney weights, and increased incidences of microscopic changes in kidney and liver in males at 320 mg/kg/day (the highest dose group).

#### **C. Classification of Carcinogenic Potential**

In 1990, the HED RfD/Peer Review Committee classified butylate as a **Group E** Chemical (no evidence of carcinogenicity for humans) based on lack of evidence of carcinogenicity in mice (HED Doc. No. 003070 and 003830) and rats (HED Doc. No. 004590 and 005795). The HIARC concurred with this classification.

#### IV. MUTAGENICITY

Butylate was negative for inducing mutations in all acceptable guideline studies of the standard battery of mutagenicity tests. Thus, in the Ames assay, butylate was negative for inducing reverse mutation in four histidine-requiring strains of Salmonella typhimurium at doses up to the limit of solubility (5 uL/plate) under both nonactivation and two sources of metabolic activation (rat and mouse S9) (MRID No. 00162707). In the mouse lymphoma multiple endpoint test (forward mutation assay part), no increase in mutant colonies was found in mouse lymphoma cells treated with butylate up to levels producing excessive toxicity (relative cell survivals of 10-25%), in either the presence or absence of metabolic activation (MRID No. 00162708). In the cytogenetic portion of the mouse lymphoma multiple endpoint test (cytogenetic assay), butylate applied to mouse lymphoma cells induced dose-related sister chromatid exchanges under activation conditions only, but no chromosome aberrations with or without activation up to toxic levels (MRID No. 00162709). The interpretation and biological significance of sister-chromatid exchanges are unknown at this time.

Butylate was also tested in accessory non-guideline studies, with negative results. Butylate failed to increase gene conversions in the D4 strain of the yeast, Saccharomyces cerevisiae, at either nonactivated or activated doses up to 5.0 uL/mL (limit dose) (MRID No. 00149317). In the transformation assay, butylate was negative for the ability to transform BALB/3T3 cells, even at concentrations producing severe toxicity (MRID No. 00162710).

#### V. FQPA CONSIDERATIONS

##### 1. Neurotoxicity:

In an **acute neurotoxicity screening study** (MRID Nos. 43514101 and 43967901), butylate technical (95.7% a.i.) in corn oil was administered to Sprague-Dawley rats (10/sex) by oral intubation at single doses of 0, 200, 600, or 2000 mg/kg. **The NOEL for acute neurotoxicity was 600 mg/kg. The LOEL for acute neurotoxicity was 2000 mg/kg based on sciatic nerve effects, neuronal cell necrosis, body weight decrease, and clinical signs of toxicity.** This study is discussed in detail in Section I, Acute Reference Dose. This study is acceptable/guideline and satisfies the guideline data requirement for an acute neurotoxicity screening battery (81-8).

In a **subchronic neurotoxicity screening battery** (MRID No. 43452201), butylate (95.7% a.i.) was administered to APfSD rats (12/sex/dose) in the diet at concentrations of 0, 250, 1000 or 5000 ppm for 13 weeks. Mean calculated doses of butylate given to rats were equivalent to nominal intakes of 0, 18.7, 76.0, or 366.1 mg/kg/day for male groups, respectively and 0, 21.5, 80.6, or 382.5 mg/kg/day for female groups, respectively. Neurological functions [functional observation battery (FOB) and locomotor activity (LA)] were monitored monthly (study weeks 5, 9, 14). There was evidence of systemic toxicity in the form of decreased body weight and food consumption at 5000 ppm for males and females. Body weight was statistically significantly reduced in the 5000 ppm males (6-9%) and females (7-12%) at most weekly measurements. Body weight was statistically significantly reduced in the 2500 ppm females (5-8%), however, the

body weight decreases were relatively minimal and not considered toxicologically significant. Food consumption was statistically significantly reduced in the 5000 ppm males (10-15%) and females (12-23%) at most weekly intervals. There were no compound-related changes recorded in brain, plasma or erythrocyte cholinesterase activities nor in neuropathy target esterase activity. No evidence of either structural (organic) or functional (FOB/LA) impairment of the nervous system was found up to the highest dose tested (5000 ppm). **The NOEL for subchronic neurotoxicity was equal or greater than 5000 ppm. The LOEL for subchronic neurotoxicity was not identified.** This study is acceptable/guideline and satisfies the guideline data requirement for a subchronic neurotoxicity screening battery (82-7).

## 2. Developmental Toxicity

### (I) Rat

In a developmental toxicity study (MRID No. 00131032), Butylate technical (98.2%) was administered to female Sprague-Dawley rats (26/dose) by oral intubation at doses of 0, 40, 400, or 1000 mg/kg/day from gestation days 6 through 19. **The NOEL for maternal toxicity was 40 mg/kg/day. The LOEL for maternal toxicity was 400 mg/kg/day based on decreases in body weight, body weight gain, food consumption, and an increase in relative liver weight. The NOEL for developmental toxicity was 40 mg/kg/day. The LOEL for developmental toxicity was 400 mg/kg/day based on decreased fetal weights and increased incidences of hematomas of the thoracic spinal region and misaligned sternbrae.** This study is classified Acceptable/Guideline and satisfies the guideline data requirement for a developmental study (83-3a) in rats.

### (ii) Rabbit

In a developmental toxicity study (MRID No. 40389102), Butylate technical (99%) was administered to female New Zealand White rabbits (16/dose) by oral intubation at doses of 0, 10, 100, or 500 mg/kg/day from gestation days 7 through 19. No adverse effects were seen in mothers or offspring at 100 mg/kg/day. At 500 mg/kg/day, decrease in body weight gain (48%) was found for the treated interval days 7 through 13. In addition, at 500 mg/kg/day, decrease in food consumption and increase in absolute and relative ovarian weights were found. The developmental toxicity was not observed at any tested dose. **The NOEL for maternal toxicity was 100 mg/kg/day. The LOEL for maternal toxicity was 500 mg/kg/day based on decreased body weight gain and food consumption and an increase in absolute and relative ovarian weights. The NOEL for developmental toxicity was equal to or greater than 500 mg/kg/day. The LOEL for developmental toxicity was not identified.**

**This study is classified ACCEPTABLE/GUIDELINE and satisfies the guideline data requirement for a developmental study (83-3b) in rabbits.**

## 3. Reproductive Toxicity:

In a 2-generation reproduction study (MRID No. 00160548 and 00155519), Butylate technical (98.2% a.i.) was administered to Sprague-Dawley CD rats (25/sex/dose) in the diet at concentrations of 0, 200, 1000 or 4000 ppm (equivalent to a nominal intake of 0, 10, 50, or 200 mg/kg/day, respectively).

At 4000 ppm, body weights of the parental animals of the Po generation were significantly lower (10-11% for males and 9-14% for females) compared to the controls. Also, body weights of the parental animals of the P1 generation were significantly lower (9-18% for males and 14-19% for females) compared to the controls. At this dose, food consumption of the parental animals of the Po and P1 generations were significantly lower (8-17% for males and 6-21% for females) compared to the controls at most of the reported time intervals. In addition, at this dose, there were decreased hematocrit values in Po males and females, decreased hemoglobin values in Po and P1 females, increased relative liver weights of Po males (13%), Po females (12%) and P1 females. Microscopically, there was an increased incidence of hepatocyte vacuolation in the P1 males. At 1000 ppm, body weights of dams during gestation (P1, first mating) and during lactation (P1, all matings) were significantly lower (5-8%) compared to the controls. At this dose, there were decreased food consumption of P1 males and increased relative liver weights of Po females (5%). **The NOEL for parental toxicity was 200 ppm (10 mg/kg/day); the LOEL was 1000 ppm (50 mg/kg/day) based on decreased food consumption, decreased body weights and increased liver weights (females only).**

At 4000 ppm, there was decreased litter size in the F1a, F2a, and F2b generations, decreased absolute kidney weights of F1b males (24%) and F1b females (21%), decreased absolute brain weights of F1b males (10%) and F1b females (8%), decreased kidney weights of F2c males (24%), increased relative liver weights of F2c males and females, increased incidence of dilated kidney (renal pelvis) and retinal folds in the F1b generation.

At 1000 ppm, there were decreased pup weights (8-11%) in the F2a generation on days 14 and 21 and decreased absolute brain (8%) and kidney (15%) weights of the F1b male weanlings.

**The NOEL for reproductive toxicity was 200 ppm (10 mg/kg/day); the LOEL was 1000 ppm (50 mg/kg/day) based on decreased pup weights and decreased absolute brain and kidney weights.**

**This study is classified Acceptable/Guideline and satisfies the guideline data requirement for a multi-generation reproduction study (83-4) in rats.**

4. Additional information from the literature (IF AVAILABLE)

No literature search was conducted for this chemical.

5. Determination of Susceptibility

The data provided no indication of increased susceptibility of rats or rabbits *in utero* and/or post natal exposure to butylate. In the prenatal developmental toxicity study in rats, developmental toxicity was seen in the presence of maternal toxicity. In the developmental toxicity study in rabbits, no evidence of developmental toxicity was seen even in the presence of maternal toxicity at the highest dose tested. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

6. Recommendation for a Developmental Neurotoxicity Study

Based on the available data, the HIARC concluded that a developmental neurotoxicity study **is not required**.

- i. Evidence that suggest requiring a developmental neurotoxicity study: none
- ii. Evidence that **do not** support a need for a developmental neurotoxicity study:

There is no evidence from the developmental studies, or reproduction study that there would be potential for developmental neurotoxicity. No evidence of treatment-related anomalies in the development of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic oral doses up to 1000 or 500 mg/kg/day, respectively. [In the rat study, one fetus with microencephaly was observed at the LDT of 40 mg/kg/day, and in the rabbit study, dilation of the hindbrain was observed in 2 fetuses of one control litter and 2 fetuses of 2 LDT (10 mg/kg/day) litters.]

There was no evidence of treatment-related behavioral toxicity in the chronic studies in dogs, rats, or mice. No effects on brain weight or histopathology of the brain (in nonperfused tissues) were observed in any of the guideline studies in which these parameters were measured. Although absolute and relative thyroid/parathyroid weights were increased in the chronic dog study at the HDT of 100 mg/kg/day, this finding was not observed across both sexes, nor was it observed in any other study.

No effect on histopathology of perfused tissues of the nervous system was observed in the subchronic neurotoxicity study in rats, and NTE was negative.

Butylate is not a potent toxicant. It has an oral LD<sub>50</sub> of 4850 mg/kg in male rats and 4785 mg/kg in female rats.

7. Determination of the FQPA Safety Factor:

The HIARC, based on hazard assessment alone, recommends to the FQPA Safety Committee, that the additional 10 x factor should be removed because of the following reasons:

- a. Developmental toxicity studies showed no increased sensitivity in fetuses as

compared to maternal animals following *in utero* exposures in rats and rabbits.

- b. A two-generation reproduction toxicity study in rats showed no increased susceptibility in pups when compared to adults.
- c. There was no evidence of abnormalities in the development of fetal nervous system in the pre/post natal studies in either rats or rabbits. Neither brain weight nor histopathology (perfused or nonperfused) of the nervous system was affected in the subchronic or chronic toxicity studies.
- d. The toxicology data base is complete and there are no data gaps. There is no evidence to require a developmental neurotoxicity study.

The final recommendation on the FQPA Safety Factor, however will be made during the risk characterization by the FQPA Safety Committee.

## **VI. HAZARD CHARACTERIZATION**

The data base is complete and all of the toxicology studies are acceptable and satisfy the Subdivision F Hazard Evaluation Guidelines.

There is high confidence in the chronic RfD, which received agency-wide consensus and is available on IRIS. In the critical study, NOEL was 5 mg/kg/day from chronic feeding study in dogs. The LOEL was 25 mg/kg/day based on decreased body weight gain (not statistically significant) and increased relative liver weight in male dogs which is the most sensitive endpoint following chronic exposure. The NOEL for systemic toxicity in female dogs was 25 mg/kg/day and the LOEL was 100 mg/kg/day based on decreased body weight gain, changes in clinical pathology parameters and increased absolute and relative liver weights and thyroid/parathyroid weights.

There is no evidence that butylate is neurotoxic, and no additional studies are required, including a developmental neurotoxicity study.

There is no evidence for increased susceptibility of rat or rabbit fetuses to *in utero* exposure in developmental studies. The maternal and parental NOELs were less than or equivalent to the offspring NOELs. In the developmental toxicity study in rats, the maternal NOEL, based upon decreased body weight, body weight gain and food consumption and an increase in relative liver weight, was equivalent to the developmental NOEL (40 mg/kg/day), which was based upon decreased fetal weights, and variations including increased incidence of hematomas and misaligned sternebrae. In the developmental toxicity study in rabbits, no developmental toxicity was noted at a high dose level (500 mg/kg/day) which produced maternal toxicity (decreased body weight, decreased food consumption, and increased ovarian weights). In the two-generation reproduction study, effects in the offspring (decreased pup weights and decreased absolute brain and kidney weights) were observed at the same dietary levels (50 mg/kg/day) which produced

decreased body weight and food consumption and increased female liver weights in the adults. In conclusion, there is no increased susceptibility for infants and children based on an adequate data base, no evidence of neurotoxicity, and the results from the developmental/reproductive toxicity studies.

## **VII. DATA GAPS**

The toxicology data base is complete for butylate; there are no data gaps.

## **VIII. ACUTE TOXICITY ACUTE TOXICITY ENDPOINTS**

### **Acute Toxicity of Butylate**

<b>Guideline No.</b>	<b>Study Type</b>	<b>MRIDs #</b>	<b>Results</b>	<b>Toxicity Category</b>
81-1	Acute Oral (rats)	254690	LD <sub>50</sub> = 4850 mg/kg (males) LD <sub>50</sub> = 4785 mg/kg (females)	III
81-2	Acute Dermal (rabbits)	254690	LD <sub>50</sub> > 5000 mg/kg (males and females)	IV
81-3	Acute Inhalation	42389401	LC <sub>50</sub> >1.64mg/L	III
81-4	Primary Eye Irritation	254690	No irritation	IV
81-5	Primary Skin Irritation	254690	Mild irritation	IV
81-6	Dermal Sensitization	42123903	Mild skin sensitizer	
81-8	Acute Neurotoxicity (rats)	43514101 and 43967901	NOEL= 600 mg/kg. LOEL = 2000 mg/kg based on sciatic nerve effects, neuronal cell necrosis, body weight decrease, and clinical signs of toxicity (salivation, and tip-toe gaits, lacrimation, oral-nasal staining, urinary incontinence).	

## IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Female 13+)	Developmental NOEL=40	Decreased fetal weights and increased incidences of misaligned sternebrae	Developmental–rat
	UF=100	<b>Acute RfD=0.4 mg/kg/day</b>	
Acute Dietary (General population including Infants and Children)	Acute neurotoxicity NOEL=600	Sciatic nerve effects, neuronal cell necrosis, body weight decrease, and clinical signs of toxicity	Acute neurotoxicity–rat
	UF=100	<b>Acute RfD=6 mg/kg/day</b>	
Chronic Dietary	NOEL=5	Increased relative liver weight in male dogs	12-Month feeding–dog
	UF=100	<b>Chronic RfD=0.05 mg/kg/day</b>	
Short-Term (a) (Dermal)	Developmental NOEL=40	Decreased fetal weights and increased incidences of misaligned sternebrae	Developmental–rat
Intermediate-Term (a) (Dermal)	Developmental NOEL=40	Decreased fetal weights and increased incidences of misaligned sternebrae	Developmental–rat
Long-Term (Dermal)	None	Not required under the registered use patterns	
Inhalation (b) (Short & Intermediate)	Developmental NOEL=40	Oral NOEL was selected due to lack of appropriate inhalation studies. See Section III.5 for details	
Inhalation (Long-Term)	None	Not required under the registered use patterns	

a = Since oral NOELs were selected a dermal absorption factor of 100% should be used in route-to-route extrapolation.

b = Since oral NOELs were selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.